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Substituent Strength Vs Reactivity: A Study Of 1,3,4-Oxadiazoles And Electron Donating Groups

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SUBSTITUENT STRENGTH VS REACTIVITY:
A STUDY OF 1,3,4-OXADIAZOLES AND ELECTRON DONATING GROUPS

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Abstract

This investigation focused on determining if there was a relationship between electron donating group substituent strength and resulting percent yield values of the 1,3,4-oxadiazole product. The data obtained from this investigation aimed to help chemists better understand the reactivity of the 1,3,4-oxadiazole because of its importance in the realm of drug design and development. In order to accomplish this, electron donating groups with varying pKa values were placed on the 1,3,4-oxadiazole and the resulting percent yields were analyzed for possible trends. The substituents used represented both resonance donating and inductively donating groups and were placed in both ortho and para positions to demonstrate possible steric effects. A direct correlation between electron donating strength and percent yield was not found, but the data did show lesser yield values when compared to similar reactions involving electron withdrawing groups.

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Introduction

Heterocycles are molecules that have great importance in biological function and pharmaceuticals[1]. Their use in drug design is widespread and proves to be vital in the fight against many life-altering diseases. A heterocycle includes a group of carbon atoms arranged in a ring that also contains a heteroatom—any atom that is not carbon[2,3]. There are many naturally occurring heterocycles that are created through biosynthesis. Familiar ones include the neurotransmitter, serotonin, and the vitamin, folic acid[4]. These examples are both displayed in figure 1.

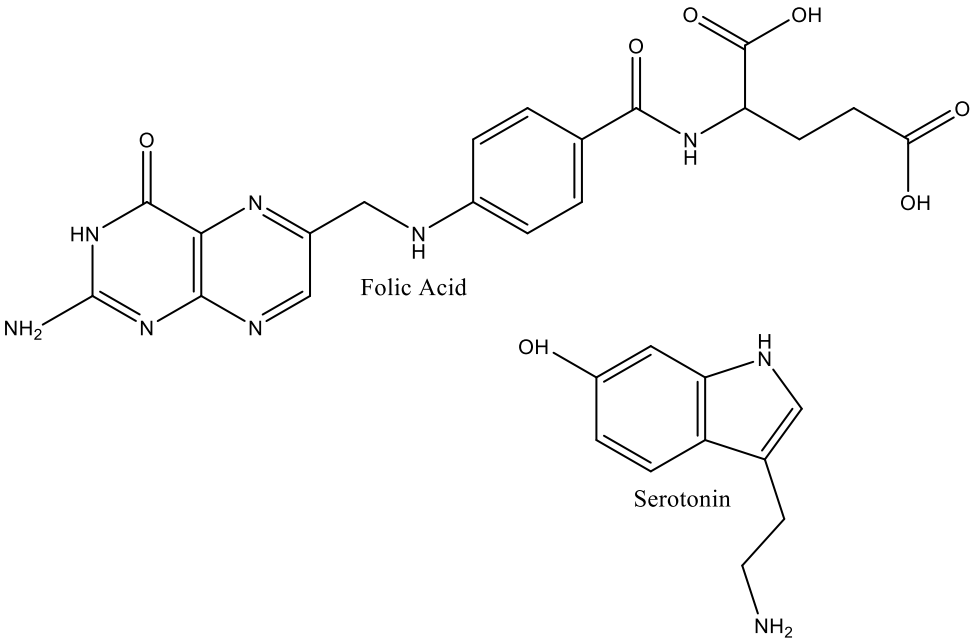
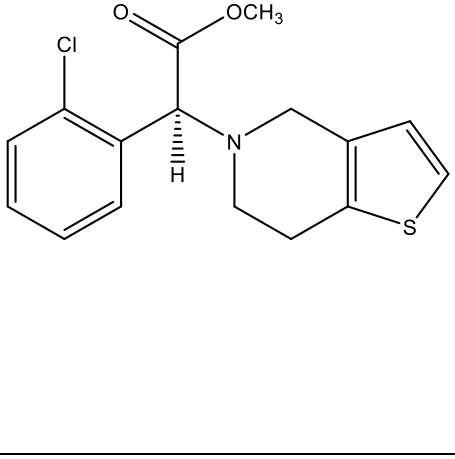
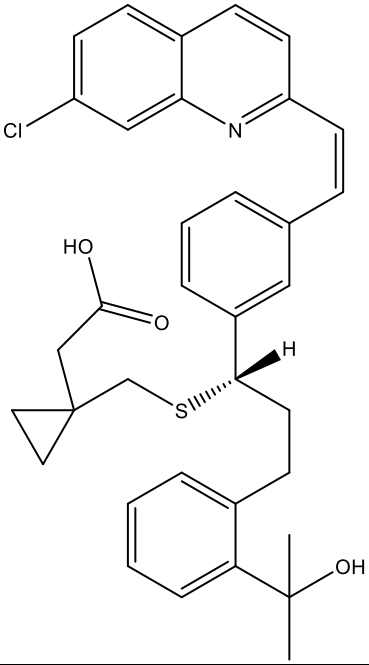


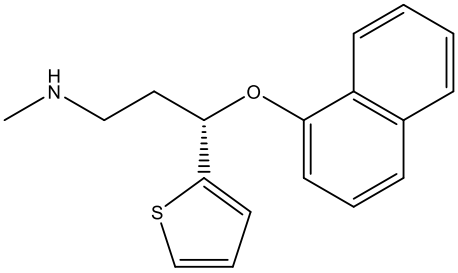
Figure 1. Naturally Occurring Heterocycles

Heterocycles that are used in drug design usually do not occur naturally and have to be created in a laboratory using other smaller molecules. A heterocycle's importance in the realm of

pharmaceuticals is not modest—they can be found in all top ten brand name small molecule drugs. A few examples include Cymbalta (antidepressant), Singulair (antiashmatic), and Plavix (platelet aggregation inhibitor)[5] shown in figure 2.







Plavix	**Singulair**	**Cymbalta**

Figure 2. Drugs that Contain Heterocycles

One type of heterocycle of interest is the oxadiazole. Oxadiazoles contain a five-membered heterocyclic ring structure with two carbon atoms, two nitrogen atoms, and one oxygen atom[6]. Oxadiazoles have been shown to have anticancer[7,8], anti-inflammatory[3,9], and antifungal activity[3]. There are many drugs in late clinical trials that contain oxadiazoles. Among them are zibotentan, an anticancer agent, and ataluren, a treatment of cystic fibrosis. Raltegravir is an antiretroviral drug that also contains an oxadiazole and is used for the

treatment of HIV infection. It has moved passed clinical trials and has been launched onto the market-place[6]. The one structural feature that sets heterocycles like oxadiazoles apart from other compounds is their ability to manifest substituents—any group on a molecule[10]—around a core scaffold in a defined three dimensional representation[11].

Oxadiazoles can be synthesized through a cyclo-dehydration reaction in which a hydrazide and carboxylic acid are combined. The general reaction scheme is shown in figure 3.

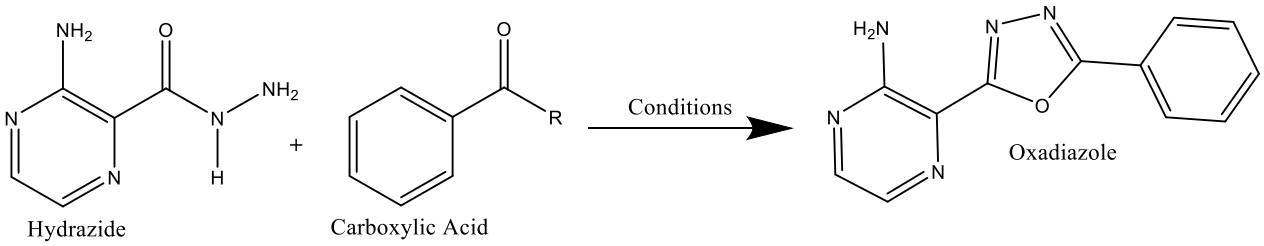


Figure 3. General Oxadiazole Synthesis

Four different reactions involving the synthesis of the 1,3,4-oxadiazole were previously investigated using various reaction conditions. The first reaction used dibromotriphenylphosphorane and acetonitrile as the reaction conditions. This reaction required a nitrogen atmosphere and increased the purity of the final product. The second reaction involved triethyl orthoformate and was difficult to preform due to the high boiling point of triethyl orthoformate; the system had a tendency to dry out and burn up while refluxing overnight. The third reaction used phosphorous oxychloride and produced no product. Lastly, the final reaction was the only one investigated that used an aldehyde instead of a

carboxylic acid—the R shown in figure 3 was a hydrogen instead of the typical alcohol. It also used ceric ammonium nitrate and dry dichloromethane as the reaction conditions and produced the highest yield of product which was pure after a recrystallization was performed. Although the synthesis of the 1,3,4-oxadiazole can be achieved with a variety of reagents, the previous research concluded that dibromotriphenylphosphorane and acetonitrile provided the best reaction conditions. This was due to its increased purity of the final product[5]. Increased purity is important because it is not uncommon for methods of heterocyclic formation to produce large amounts of waste and small amounts of product[4].

Modifying physical and chemical properties of molecules via substitution of electron donating and withdrawing groups is an active area of research. Researchers have explored the environment of reactive sites by employing artificial molecules with different electron donating and electron withdrawing groups and analyzing the effects[7,12]. The data obtained from these analyses is important regarding newer reactions because it gives scientists the ability to determine which chemical environments the reactions work best under. In other words, if it is found that certain substituents slow a reaction's progression, then scientists know to avoid their use in the future. It has been found that electron donating groups (EDGs) tend to destabilize transition states by donating electrons into a reaction center and retarding reactions. Electron withdrawing groups (EWGs), on the other hand, tend to stabilize transition states by withdrawing electrons from a reaction center and speeding up reactions. The reaction center of this study is the carbonyl carbon of benzoic acid. The effects of some EDGs and EWGs on this particular reaction center can be seen in figure 4 which displays both resonance and inductive effects.

A resonance effect is the donation or withdrawal of electrons through neighboring pi systems and involves the distribution of electrons. This can be seen in structures A and C in figure 4. In structure A, the lone-pair electrons on the methoxy group (-OCH_3) are able to flow from the substituent towards the ring thus eventually making the carbonyl carbon more negative. Amino groups (ex: -NH_2, -NR_2) also act in this manner. On the other hand, in structure C, the nitro group (-NO_2) causes pi electrons to flow from the ring to the substituent resulting in the carbonyl carbon becoming more positive. An example of another EWG that acts similarly is a nitrile group (-CN). Whether or not a substituent causes electrons to flow towards or away from it depends on electronegativity[13].

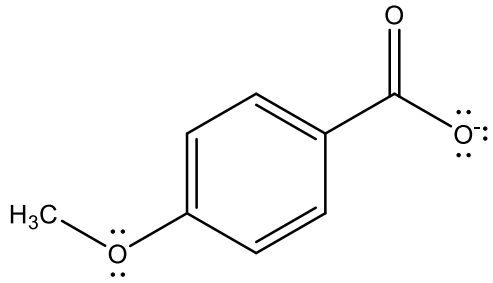
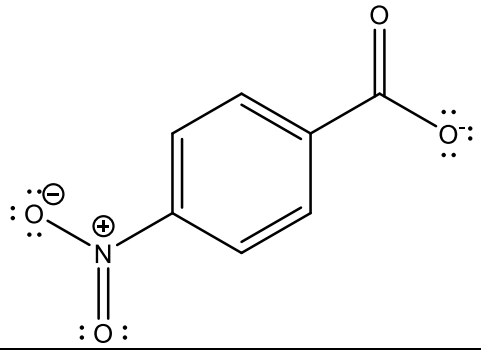
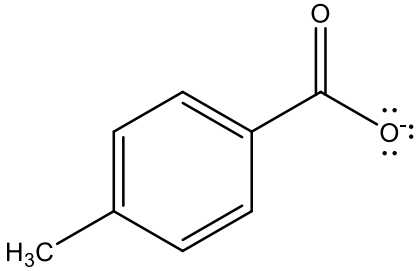
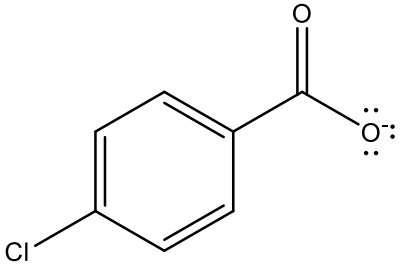
Electron-Donating	**Electron-Withdrawing**
	
Structure A Resonance Donating	**Structure C** Resonance Withdrawing
	
Structure B Inductively Donating	**Structure D** Inductively Withdrawing

Figure 4. Effects of EDGs and EWGs

Electronegativity is a chemical property that describes an atom's tendency to attract electrons towards itself. It is affected by an atom's atomic number and the distance between an atom's valence electrons and its charged nucleus. Atoms or substituents that are more electronegative pull electrons towards them. Structures B and D in figure 4 represent EDG and EWG inductive effects, respectively. Unlike how resonance effects involve pi bonds, inductive effects are the direct withdrawal or donation of electrons through sigma bonds due to electronegativity. In structure B, the methyl group ($-CH_3$) is poorly electronegative so it inductively donates electrons to the ring. In structure D, the chloro group (-Cl) is highly electronegative and inductively withdrawals electrons from the ring. Other halogens that act in this way include bromine (-Br) and the most electronegative atom on the periodic table, fluorine (-F)[13].

The effect of substituents are also influenced by their position in relationship to other substituents. Chemists use the prefixes ortho, meta, and para to name disubstituted benzenes and to describe the location of the substituents. Ortho, meta, and para can also be represented by the numbers 2, 3, and 4, respectively. An ortho-disubstituted benzene has two substituents in a 1,2 relationship on the ring. A meta-disubstituted benzene has two substituents in a 1,3 relationship. Lastly, a para-disubstituted benzene has its substituents in a 1,4 relationship. These relationships are displayed in figure 5. The location of substituents can produce effects that are known as steric effects. Steric effects impact whether certain collision paths are favored or disfavored during the course of a reaction[13]. The information gained from analyzing the effects of substituents is used to determine how the free energy of a reaction—the minimum energy required to start a chemical reaction—varies as a function of chemical

structure. In other words, scientists are curious to learn how various substituents change the reactivity of a molecule.

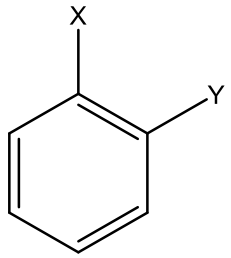
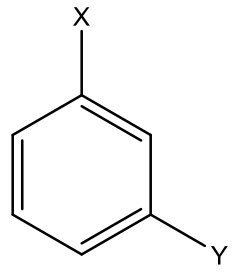
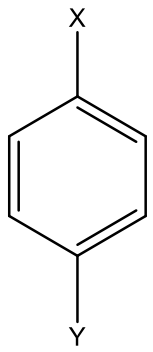
		
Ortho	**Meta**	**Para**

Figure 5. Ortho/Meta/Para

To study the correlation between structure and reactivity, the Hammett equation was developed. Chemists use the Hammett equation to specifically look at the relationship between structure and both the equilibrium and reaction rate constants for reactions of certain substituted benzene derivatives[14]. Hammett plots provide a visualization of how reaction mechanisms are affected by electronic changes induced by substituents[10]. The equilibrium constant (Keq) is a ratio of the concentration of the products to the concentration of the reactants in a reaction. The rate constant (k) quantifies the rate of a reaction and is dependent on the activation energy. A Hammett plot provides evidence of how substituents affect the speed of reactions by directly measuring Keq. Instead of examining substituent effects on Keq,

this study investigated whether or not there was a relationship between the strength of EDG substituents and percent yield values.

To investigate this possible relationship, EDGs of varying strength were placed as substituents on the benzoic acid used to synthesize the 1,3,4-oxadiazole. The strength of each EDG was determined by pKa values. pKa values are related to equilibrium constants. When working with acids, chemists refer to equilibrium constants as acid-dissociation constants, Ka values. These values are typically miniscule so chemists express Ka values as pKa values where pKa is equal to the negative logarithm of Ka. Stronger acids have smaller pKa values whereas weaker acids have larger pKa values. EDGs are stronger the less acidic that they are; therefore the strongest EDGs have higher pKas[13]. The acids that were used in this study and their pKa values are displayed in figure 6.

As previously stated, the reaction center of this particular reaction is the carbonyl carbon located on the benzoic acid. This carbon acts as an electrophile due to its partial positive charge. An electrophile is a reagent that is attracted to negatively charged electrons. Positive and negative charges attract one another. When EDGs are employed, the reaction center is thought to become less electrophilic and less reactive due to the donation of elections. The resulting yields following the addition of different EDG substituents were examined to determine whether or not stronger EDGs produced lower yields as expected. When looking at this information from a drug design standpoint, it could help provide a better understanding of which direction to take when designing a particular drug containing oxadiazole moieties.

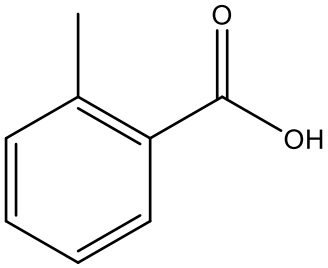
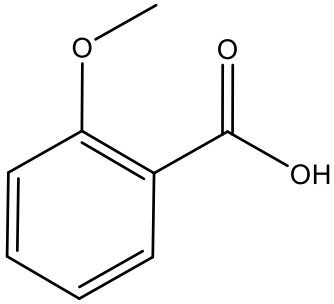
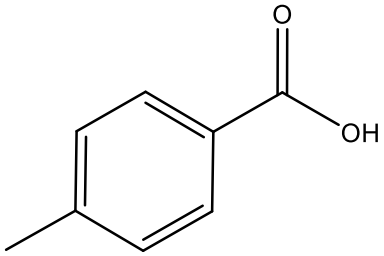
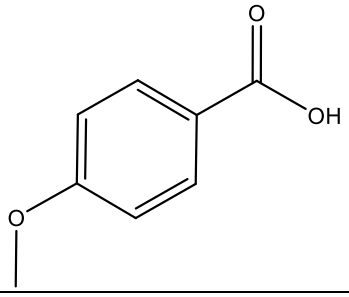
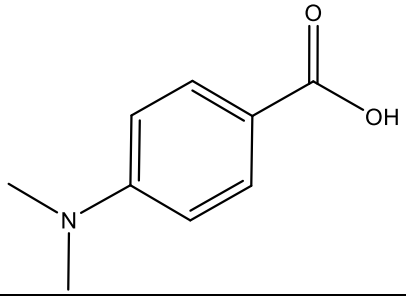
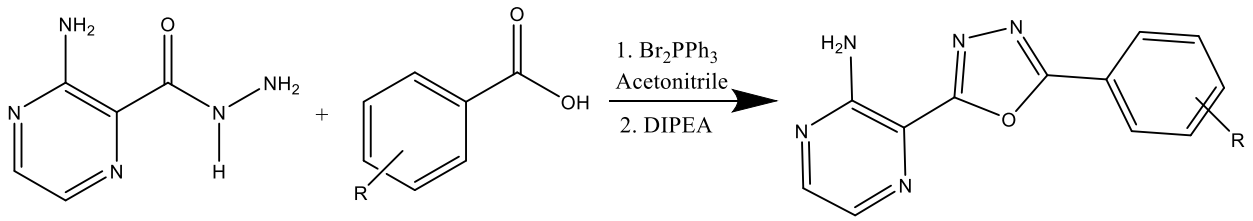
Starting Acid	Structure	pKa Value
2-toluic acid		3.95
2-methoxy benzoic acid		4.09
4-toluic acid		4.37
4-methoxy benzoic acid		4.47
4-dimethylamino benzoic acid		4.91

Figure 6. Acids Used

Data & Results

This investigation aimed to determine whether or not stronger EDG substituents produced lower yields of the 1,3,4-oxadiazole. Figure 7 summarizes the results and displays the resulting yield values for each carboxylic acid. Each reaction was repeated more than once so the yield values listed are averaged. For each of the ortho/para pairs in figure 7, the ortho



R	pKa Value	% Yield
2-CH_3	3.95	3.5
2-OCH_3	4.09	17.5
4-CH_3	4.37	9.9
4-OCH_3	4.47	61.9
4-$N(CH_3)_2$	4.91	21.5

Figure 7. Averaged Results

substituents produced lower yields. This is likely due to the EDG being closer to the reaction center and thus producing a greater electron-donating effect. Overall, however, figure 7 does not show a direct decrease in yield values as pKa values increase. It is possible that the pKa values in this study do not represent a wide enough range to show the relationship that was predicted. A future study may have more success with a wider variety of pKa values.

A more detailed analysis of the results can be found in figure 8 which shows the yields of each reaction instead of the average. There is large variability in yield values for both the ortho-

R	pKa	% Yield 1	% Yield 2	% Yield 3	% Yield 4
2-CH_3	3.95	4.6	2.3	X	X
2-OCH_3	4.09	0.0	25.9	9.0	21.6
4-CH_3	4.37	9.2	10.6	X	X
4-OCH_3	4.47	47.4	73.3	65.0	X
4-$N(CH_3)_2$	4.91	39.1	4.4	0.0	X

Figure 8. Detailed Results

methoxy and para-amino groups. This variability is due to errors that occurred during the reactions. For the ortho-mexothy's first yield, no product was formed due to the flask being improperly put under nitrogen. The para-amino's second yield was determined after a recrystallization was performed thus loss of product likely occurred. The last two yields of the para-amino were recorded as being "sticky" and "clumped" which signifies contamination or an improper reaction. During the para-amino's last reaction, the stir bar failed to stir properly overnight and likely resulted in a failed reaction with no yield. These errors could have produced inaccurate results.

It is also possible that unreliable reaction conditions affected the results of this study. It was mentioned previously that prior research determined the best reaction conditions for the synthesis of the 1,3,4-oxadiazole included dibromotriphenylphosphorane which is represented as Br_2PPh_3 in figure 7. While performing these reactions, it was repeatedly noted that dibromotriphenylphosphorane is exceptionally sensitive to water. As a result of this, dibromotriphenylphosphorane decomposes rapidly. It can be hypothesized that the yield values

in this study were influenced by the age of the dibromotriphenylphosphorane used. Newer bottles could have produced higher yields whereas older bottles could have caused unreliable results. It would be vital for future studies to take this information into account.

Although this study did not show a direct correlation between stronger EDG substituents and lower yield values, when compared to the EWG substituents the yields were vastly lower as a whole. Parallel reactions that were run with EWG substituents had yield values that ranged from 45% to 89% which were significantly higher. Although this investigation did not prove a direct relationship between EDG pKa and yield, it did further show that EDG substituents lessen the percent yield of the 1,3,4-oxadiazole overall. This information is useful because when designing drugs containing oxadiazoles, chemists may stray from EDG substituents to avoid low yields of product.

Materials & Methods

Hydrazide Synthesis

Methyl-3-amino-2-pyrazine carboxylate (13.0 mmol) and 87 mL absolute ethanol were added to roundbottom flask. Hydrazine monohydrate (3.8 mL, 78.3 mmol) was then added to the flask via a syringe. The flask was equipped with a stir bar and clamped in a hot oil bath for 1.5 hours. Once finished, the flask was taken from the oil bath to cool. After cooling, the product was filtered through sintered glass and washed with ethanol and then water and dried overnight[15]. 78.5% yield.

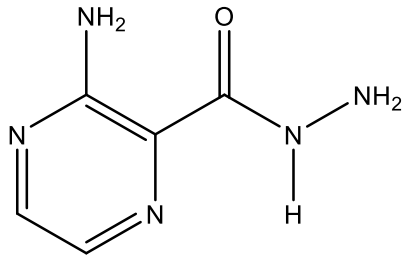


Figure 9. **Acyl Hydrazide.** 78.5% Yield**.**

1,3,4-Oxadiazoles

In a roundbottom flask, acyl hydrazide (0.862 mmol) and benzoic acid (0.862mmol) were added. The flask was flushed with nitrogen and equipped with a stir bar. 4 mL of acetonitrile were added and the solution was set to begin stirring. Following this, dibromotriphenylphosphorane (4.137 mmol) was then added to the flask and the solution was left to stir for one hour. At the end of the hour, diisopropylethylamine (0.9 mL) was added to the flask and the resulting solution continued stirring overnight. The following day approximately 18 hours later, the flask was removed from the stir plate and the solution was filtered through a sintered glass funnel using both filter paper and a vacuum. The filtered solid was washed with acetonitrile (20 mL) and hexane (10 mL) and then dried overnight using phosphine oxide[15].

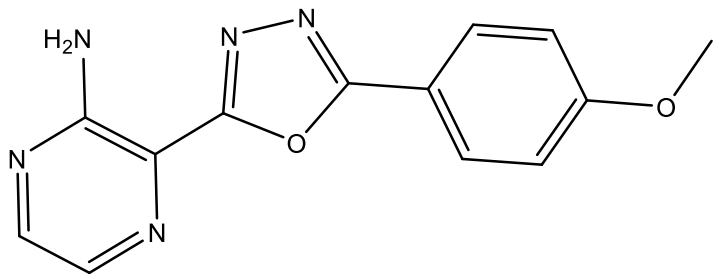


Figure 10. **4-Methoxyphenyl Oxadiazole**. 61.9 Average % Yield (47.4%, 73.3%, 65.0%).

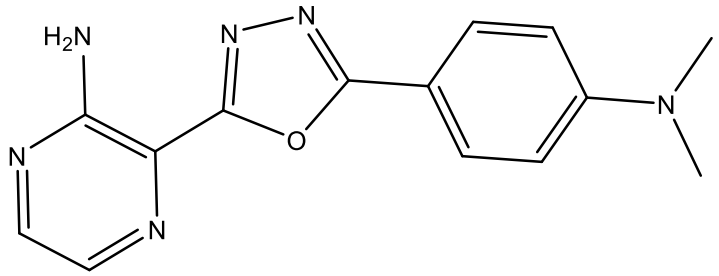


Figure 11. **4-Dimethylamino Oxadiazole.** 21.5 Average % Yield (39.1%, 4.4%).

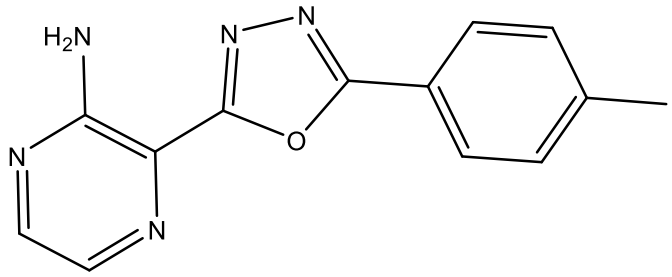


Figure 12. **4-Methylphenyl Oxadiazole.** 9.90 Average % Yield (9.2%, 10.6%).

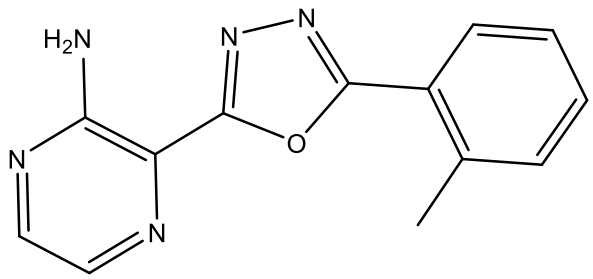


Figure 13. **2-Methylphenyl Oxadiazole.** 3.50 Average % Yield (4.6%, 2.3%).

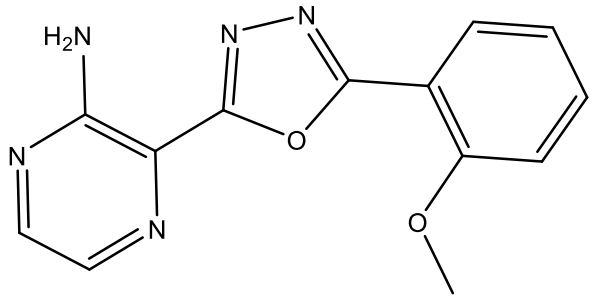


Figure 14. **2-Methoxyphenyl Oxadiazole.** 17.5 Average % Yield (25.9%, 9.0%, 21.6%).

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